

REMARKS

In view of the foregoing amendments and the following representations, reconsideration and allowance of the above-identified application is respectfully requested. Claims 1, 4-17 and 20-24 are pending in the present application.

In the Office Action, the Examiner objected to claim 7 because the term "osmopolymer" was misspelled. Applicants have corrected this error. Applicants have also amended claims 8, 9 and 20 to correct another typographical error.

In the Office Action, the Examiner rejected claims 1-33 under 35 U.S.C. § 103(a) as being unpatentable over Sackler, et al., United States Patent No. 5,478,577 (hereinafter "Sackler") in further view of Saslawski et al., United States Patent No. 6,372,255 (hereinafter "Saslawski").

In response to this rejection and in an effort to expedite prosecution of the present application, Applicants have amended independent claims 1 and 17 to recite a sustained released oxycodone formulation that comprises a core, delayed release coating around the core and an immediate release oxycodone coating applied to the delayed release coating. Applicants have further amended independent claims 1 and 17 to indicate the delayed release coating consists of a pH dependent material and an inert processing aid wherein the pH dependent material consists of two enteric agents. The first enteric agent dissolves or degrades at a pH of about 5 to 7 and the second enteric agent dissolves or degrades at a pH higher than 7. No new matter is added by the amendments. Support can be found

in the claims as originally filed, specifically claims 3, 10, 11, 19, 21 and 22. Support for the weight percents of the pH dependent material, inert processing aid and plasticizer can be found on page 6, lines 22-24 and page 7, lines 18-20 and 24-27. Applicants have also amended dependent claims 10-12 and 21-22 to conform the language to amended claims 1 and 17.

Applicants respectfully submit that the presently amended claims are patentable over the Sackler reference either alone or combined with Saslawski reference.

The present invention as recited in the pending claims is patentable over the cited references because the Applicants have surprisingly discovered a sustained release oxycodone formulation that provides safe therapeutic levels of oxycodone over a period of time by using a unique combination of pH **dependent** coating materials. Neither of the cited references relies primarily upon pH dependent agents to control the release of the active pharmaceutical dosage form. More importantly neither of the cited references even suggests the combination of two enteric agents that dissolve or degrade at separate and distinct pH values as required by the pending claims.

The Sackler reference discloses an opioid formulation designed to provide large peak to trough plasma concentrations of the opioid over a 24 hour time period. The dosage form described in the Sackler reference is designed to release the opioid at a rate that is **independent** of pH. Col. 7, lines 46-48. This is the exact opposite to the pH dependent dosage form recited in the pending claims.

The Examiner asserts that Sackler discloses a first enteric coating agent in Col. 8, lines 15-19 and a second enteric coating agent in Col. 13, lines 18-21. Col. 8, lines 15-19 describes a long list of preferred acrylic polymers that can be used to prepare the disclosed sustained release coating. Applicants respectfully submit that this section of Sackler which discloses many acrylic polymers would not lead an individual of ordinary skill to select a combination of enteric polymers as recited in the pending claims. First, many of the acrylic polymers recited in the long list in Col. 8 are not enteric polymers. Most are pH independent polymers. This fact is confirmed by Exhibit A which is a copy of the Handbook of Pharmaceutical Excipients entry for acrylic polymers. Further, all the working examples in the Sackler reference employ Eudragit RS and/or RL which are types of pH independent sustained release polymers.

Applicants agree with the Examiner that Col. 13, lines 18-21 of Sackler mentions shellac and zein and that these materials are enteric agents. However, shellac and zein are only mentioned as being part of a water insoluble polymeric coating, not a pH dependent coating as required by the claims.

Based upon the working examples and the specific statements in the Sackler reference that the drug release is pH independent, it is respectfully submitted that an individual of ordinary skill in the art would not read the disclosure in Col. 8 as teaching the use of two enteric polymers. Therefore, Applicants respectfully submit that the pending claims are patentable over the Sackler reference because the pending claims require a pH dependent coating to control the release of the

oxycodone and in particular a pH dependent coating that employs two separate and distinct enteric materials that dissolve or degrade at different pH's to provide a controlled release of the oxycodone.

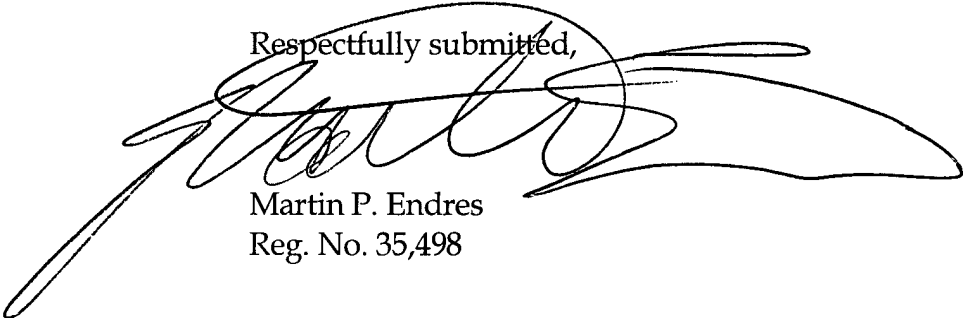
The Saslawski reference also fails to disclose or suggest a sustained release oxycodone dosage form that employs a unique pH dependent coating as recited in the pending claims. Saslawski disclose a multilayer tablet that comprises an immediate release layer and a sustained release layer. The sustained release layer disperses the active pharmaceutical ingredient in an inert polymeric matrix. Col. 1, lines 57-67. The release of the active pharmaceutical ingredient is pH independent. See: Col. 2, lines 38-31 ("The matrix of the second layer retains its physical and chemical integrity throughout the prolonged release of the active ingredient, regardless of the pH variations.") and Col. 10, line 65 to Col. 11, line 1 ("On the other hand, these copolymers are absolutely inert in relation to the body, which ensures release of the active ingredient independently of the influence of the body (and in particular of pH variations)").

In view of the clear teachings in both the Sackler and the Saslawski references to employ pH independent polymers to control the release of the drug from the disclosed dosage forms, Applicants respectfully submit that an individual of ordinary skill would not be lead to the develop a sustained release oxycodone dosage form which relies upon a unique combination of two pH dependent enteric agents to control the release of the oxycodone.

On pages 9-13 of the Office Action, the Examiner provisionally rejected claims 1-5, 7-9 and 10-26 on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over United States Patent Application No. 10/726,024. The Examiner also provisionally rejected claims 27-33 on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over United States Patent Application No. 10/726,024 in view of Campbell, United States Patent No. 6,485,746. In response to these provisional rejections, Applicants respectfully request reconsideration based upon the present amendments. If the Examiner maintains the nonstatutory double patenting rejections and finds allowable subject matter, an appropriate terminal disclaimer will be submitted.

Based upon the foregoing amendments and representations, Applicants respectfully submit that the rejection of the claims in the above-identified application have been overcome and should be withdrawn. Early and favorable action is earnestly solicited.

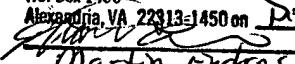
Respectfully submitted,


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Polymethacrylates

1 Nonproprietary Names

- BP: Methacrylic acid-ethyl acrylate copolymer (1:1)
Methacrylic acid-ethyl acrylate copolymer (1:1) dispersion 30 per cent
Methacrylic acid-methyl methacrylate copolymer (1:1)
Methacrylic acid-methyl methacrylate copolymer (1:2)
- PhEur: Acidum methacrylicum et ethylis acrylas polymerisatum 1:1
Acidum methacrylicum et ethylis acrylas polymerisatum 1:1 dispersio 30 per centum
Acidum methacrylicum et methylis methacrylas polymerisatum 1:1
Acidum methacrylicum et methylis methacrylas polymerisatum 1:2
- USPNF: Ammonio methacrylate copolymer
Methacrylic acid copolymer
Methacrylic acid copolymer dispersion

Note that three separate monographs applicable to polymethacrylates are contained in the USPNF 20; see Section 9. Several different types of material are defined in the monographs. The PhEur 2002 contains four separate monographs applicable to polymethacrylates.

2 Synonyms

Eastacryl 30D; *Eudragit*; *Kollicoat MAE 30 D*; *Kollicoat MAE 30 DP*; polymeric methacrylates.

3 Chemical Name and CAS Registry Number

See Table I.

4 Empirical Formula and Molecular Weight

The PhEur 2002 describes methacrylic acid-ethyl acrylate copolymer (1:1) as a copolymer of methacrylic acid and ethyl acrylate having a mean relative molecular mass of about 250 000. The ratio of carboxylic groups to ester groups is about 1:1. It may contain suitable surfactants such as sodium dodecyl sulfate or polysorbate 80. An aqueous 30% w/v dispersion of this material is also defined in a separate monograph. Methacrylic acid-methyl methacrylate copolymer (1:1) is described in the PhEur 2002 as a copolymer of methacrylic acid and methyl methacrylate having a mean relative molecular mass of about 135 000. The ratio of carboxylic acid to ester groups is about 1:1. A further monograph in the PhEur 2002 describes methacrylic acid-methyl methacrylate copolymer (1:2), where the ratio of carboxylic acid to ester groups is about 1:2.

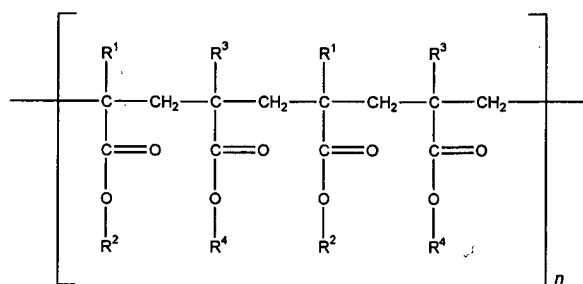
The USPNF 20 describes methacrylic acid copolymer as a fully polymerized copolymer of methacrylic acid and an acrylic or methacrylic ester. Three types, Type A, Type B, and Type C, are defined in the monograph. They vary in their methacrylic acid content and solution viscosity. Type C may contain suitable surface-active agents. Two additional polymers, Type A (*Eudragit RL*) and Type B (*Eudragit RS*), also referred

to as ammonio methacrylate copolymers, consisting of fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups, are also described in the USPNF 20. A further monograph for an aqueous dispersion of Type C methacrylic acid copolymer is also defined.

See Section 9.

Typically, the molecular weight of the polymer is $\geq 100\,000$.

5 Structural Formula



For *Eudragit E*:

$R^1, R^3 = \text{CH}_3$

$R^2 = \text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$

$R^4 = \text{CH}_3, \text{C}_4\text{H}_9$

For *Eudragit L* and *Eudragit S*:

$R^1, R^3 = \text{CH}_3$

$R^2 = \text{H}$

$R^4 = \text{CH}_3$

For *Eudragit RL* and *Eudragit RS*:

$R^1 = \text{H}, \text{CH}_3$

$R^2 = \text{CH}_3, \text{C}_2\text{H}_5$

$R^3 = \text{CH}_3$

$R^4 = \text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_3^+\text{Cl}^-$

For *Eudragit NE 30 D*:

$R^1, R^3 = \text{H}, \text{CH}_3$

$R^2, R^4 = \text{CH}_3, \text{C}_2\text{H}_5$

For *Eudragit L 30 D-55* and *Eudragit L 100-55*, *Eastacryl 30D*, *Kollicoat MAE 30 D* and *Kollicoat MAE 30 DP*:

$R^1, R^3 = \text{H}, \text{CH}_3$

$R^2 = \text{H}$

$R^4 = \text{CH}_3, \text{C}_2\text{H}_5$

6 Functional Category

Film former; tablet binder; tablet diluent.

7 Applications in Pharmaceutical Formulation or Technology

Polymethacrylates are primarily used in oral capsule and tablet formulations as film-coating agents.⁽¹⁻¹⁵⁾ Depending on the type of polymer used, films of different solubility characteristics can be produced; see Table II.

Table I: Chemical name and CAS Registry Number of polymethacrylates.

Chemical name	Trade name	Company name	CAS number
Poly(butyl methacrylate, (2-dimethyl aminoethyl) methacrylate, methyl methacrylate) 1:2:1	<i>Eudragit E 100</i>	Röhm GmbH	[24938-16-7]
	<i>Eudragit E 12.5</i>	Röhm GmbH	
Poly(ethyl acrylate, methyl methacrylate) 2:1	<i>Eudragit NE 30 D</i>	Röhm GmbH	[9010-88-2]
	(formerly <i>Eudragit 30 D</i>)		
Poly(methacrylic acid, methyl methacrylate) 1:1	<i>Eudragit L 100</i>	Röhm GmbH	[25806-15-1]
	<i>Eudragit L 12.5</i>	Röhm GmbH	
	<i>Eudragit L 12.5 P</i>	Röhm GmbH	
Poly(methacrylic acid, ethyl acrylate) 1:1	<i>Eudragit L 30 D-55</i>	Röhm GmbH	[25212-88-8]
	<i>Eudragit L 100-55</i>	Röhm GmbH	
	<i>Eastacryl 30D</i>	Eastman Chemical	[25212-88-8]
	<i>Kollicoat MAE 30 D</i>	BASF Fine Chemicals	[25212-88-8]
	<i>Kollicoat MAE 30 DP</i>	BASF Fine Chemicals	
Poly(methacrylic acid, methyl methacrylate) 1:2	<i>Eudragit S 100</i>	Röhm GmbH	[25086-15-1]
	<i>Eudragit S 12.5</i>	Röhm GmbH	
	<i>Eudragit S 12.5 P</i>	Röhm GmbH	
Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.2	<i>Eudragit RL 100</i>		[33434-24-1]
	<i>Eudragit RL PO</i>	Röhm GmbH	
	<i>Eudragit RL 30 D</i>	Röhm GmbH	
	<i>Eudragit RL 12.5</i>	Röhm GmbH	
Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.1	<i>Eudragit RS 100</i>		[33434-24-1]
	<i>Eudragit RS PO</i>	Röhm GmbH	
	<i>Eudragit RS 30 D</i>	Röhm GmbH	
	<i>Eudragit RS 12.5</i>	Röhm GmbH	

Eudragit E is used as a plain or insulating film former; it is soluble in gastric fluid below pH 5. In contrast, *Eudragit L* and *S* types are used as enteric coating agents because they are resistant to gastric fluid. Different types are available that are soluble at different pH values: e.g., *Eudragit L 100* is soluble at pH > 6; *Eudragit S 100* is soluble at pH > 7.

Eudragit RL, *RS*, and *NE 30 D* are used to form water-insoluble film coats for sustained-release products. *Eudragit RL* films are more permeable than those of *Eudragit RS*, and films of varying permeability can be obtained by mixing the two types together.

Eudragit L 30 D-55 is used as an enteric coating film former for solid-dosage forms. The coating is resistant to gastric juice but dissolves readily at above pH 5.5.

Eudragit L 100-55 is an alternative to *Eudragit L 30 D-55*. It is commercially available as a redispersible powder.

Eastacryl 30D, *Kollicoat MAE 30 D*, and *Kollicoat MAE 30 DP*, are aqueous dispersions of methacrylic acid-ethyl acrylate copolymers. They are also used as enteric coatings for solid-dosage forms.

Polymethacrylates are also used as binders in both aqueous and organic wet-granulation processes. Larger quantities (5–20%) of dry polymer are used to control the release of an active substance from a tablet matrix. Solid polymers may be used in direct-compression processes in quantities of 10–50%.

Polymethacrylate polymers may additionally be used to form the matrix layers of transdermal delivery systems and have also been used to prepare novel gel formulations for rectal administration.⁽¹⁶⁾

See also Section 18.

8 Description

Polymethacrylates are synthetic cationic and anionic polymers of dimethylaminoethyl methacrylates, methacrylic acid, and methacrylic acid esters in varying ratios. Several different types are commercially available and may be obtained as the dry powder, as an aqueous dispersion, or as an organic solution. A (60:40) mixture of acetone and propan-2-ol is most commonly used as the organic solvent. See Tables I and III.

Eudragit E is cationic polymer based on dimethylaminoethyl methacrylate and other neutral methacrylic acid esters. It is soluble in gastric fluid as well as in weakly acidic buffer solutions (up to pH ≈ 5). *Eudragit E* is available as a 12.5% ready-to-use solution in propan-2-ol-acetone (60:40). It is light yellow in color with the characteristic odor of the solvents. Solvent-free granules contain ≈98% dried weight content of *Eudragit E*.

Eudragit L and *S*, also referred to as methacrylic acid copolymers in the USP/NF 20 monograph, are anionic copolymerization products of methacrylic acid and methyl methacrylate. The ratio of free carboxyl groups to the ester is approximately 1:1 in *Eudragit L* and approximately 1:2 in *Eudragit S*. Both polymers are readily soluble in neutral to weakly alkaline conditions (pH 6–7) and form salts with alkalis, thus affording film coats that are resistant to gastric media but soluble in intestinal fluid. They are available as a 12.5% solution in propan-2-ol without plasticizer (*Eudragit L 12.5* and *S 12.5*); and as a 12.5% ready-to-use solution in propan-2-ol with 1.25% dibutyl phthalate as plasticizer (*Eudragit L 12.5 P* and *S 12.5 P*). Solutions are colorless, with the characteristic odor of the solvent. *Eudragit L-100* and *Eudragit S-100* are white free-flowing powders with at least 95% of dry polymers.

Table II: Summary of properties and uses of commercially available polymethacrylates.

Type	Supply form	Polymer dry weight content	Recommended solvents or diluents	Solubility	Applications
<i>Eudragit</i> (Röhm GmbH)					
<i>Eudragit E 12.5</i>	Organic solution	12.5%	Acetone, alcohols	Soluble in gastric fluid to pH 5	Film coating
<i>Eudragit E 100</i>	Granules	98%	Acetone, alcohols	Soluble in gastric fluid to pH 5	Film coating
<i>Eudragit L 12.5 P</i>	Organic solution	12.5%	Acetone, alcohols	Soluble in intestinal fluid from pH 6	Enteric coatings
<i>Eudragit L 12.5</i>	Organic solution	12.5%	Acetone, alcohols	Soluble in intestinal fluid from pH 6	Enteric coatings
<i>Eudragit L 100</i>	Powder	95%	Acetone, alcohols	Soluble in intestinal fluid from pH 6	Enteric coatings
<i>Eudragit L 100-55</i>	Powder	95%	Acetone, alcohols	Soluble in intestinal fluid from pH 5.5	Enteric coatings
<i>Eudragit L 30 D-55</i>	Aqueous dispersion	30%	Water	Soluble in intestinal fluid from pH 5.5	Enteric coatings
<i>Eudragit S 12.5 P</i>	Organic solution	12.5%	Acetone, alcohols	Soluble in intestinal fluid from pH 7	Enteric coatings
<i>Eudragit S 12.5</i>	Organic solution	12.5%	Acetone, alcohols	Soluble in intestinal fluid from pH 7	Enteric coatings
<i>Eudragit S 100</i>	Powder	95%	Acetone, alcohols	Soluble in intestinal fluid from pH 7	Enteric coatings
<i>Eudragit RL 12.5</i>	Organic solution	12.5%	Acetone, alcohols	High permeability	Sustained release
<i>Eudragit RL 100</i>	Granules	97%	Acetone, alcohols	High permeability	Sustained release
<i>Eudragit RL PO</i>	Powder	97%	Acetone, alcohols	High permeability	Sustained release
<i>Eudragit RL 30 D</i>	Aqueous dispersion	30%	Water	High permeability	Sustained release
<i>Eudragit RS 12.5</i>	Organic solution	12.5%	Acetone, alcohols	Low permeability	Sustained release
<i>Eudragit RS 100</i>	Granules	97%	Acetone, alcohols	Low permeability	Sustained release
<i>Eudragit RS PO</i>	Powder	97%	Acetone, alcohols	Low permeability	Sustained release
<i>Eudragit RS 30 D</i>	Aqueous dispersion	30%	Water	Low permeability	Sustained release
<i>Eudragit NE 30 D</i>	Aqueous dispersion	30% or 40%	Water	Swellable, permeable	Sustained release, tablet matrix
<i>Eastacryl</i> (Eastman Chemical Company)					
<i>Eastacryl 30 D</i>	Aqueous dispersion	30%	Water	Soluble in intestinal fluid from pH 5.5	Enteric coatings
<i>Kollicoat</i> (BASF Fine Chemicals)					
<i>Kollicoat 30 D</i>	Aqueous dispersion	30%	Water	Soluble in intestinal fluid from pH 5.5	Enteric coatings
<i>Kollicoat 30 DP</i>	Aqueous dispersion	30%	Water	Soluble in intestinal fluid from pH 5.5	Enteric coatings

Note: Recommended plasticizers for the above polymers include dibutyl phthalate, polyethylene glycols, triethyl citrate, triacetin, and 1,2-propylene glycol. The recommended concentration of the plasticizer is approximately 10–25% plasticizer (based on the dry polymer weight). A plasticizer is not necessary with *Eudragit E 12.5*, *Eudragit E 100* and *Eudragit NE 30 D*.

Eudragit RL and *Eudragit RS*, also referred to as ammonio methacrylate copolymers in the USP NF 20 monograph, are copolymers synthesized from acrylic acid and methacrylic acid esters, with *Eudragit RL* (Type A) having 10% of functional quaternary ammonium groups and *Eudragit RS* (Type B) having 5% of functional quaternary ammonium groups. The ammonium groups are present as salts and give rise to pH-independent permeability of the polymers. Both polymers are water-insoluble, and films prepared from *Eudragit RL* are freely permeable to water, whereas, films prepared from *Eudragit RS* are only slightly permeable to water. They are available as 12.5% ready-to-use solutions in propan-2-ol-acetone (60:40). Solutions are colorless or slightly yellow in color, and may be clear or slightly turbid; they have an odor characteristic of the solvents. Solvent-free granules (*Eudragit RL 100* and *Eudragit RS 100*) contain $\geq 97\%$ of the dried weight content of the polymer.

Eudragit RL PO and *Eudragit RS PO* are fine, white powders with a slight aminelike odor. They are characteristically the same polymers as *Eudragit RL* and *RS*. They contain $\geq 97\%$ of dry polymer.

Eudragit RL 30 D and *Eudragit RS 30 D* are aqueous dispersions of copolymers of acrylic acid and methacrylic acid esters with a low content of quaternary ammonium groups. The dispersions contain 30% polymer. The quaternary groups occur as salts and are responsible for the permeability of films made from these polymers. Films prepared from *Eudragit RL 30 D* are readily permeable to water and to dissolved active substances, whereas films prepared from *Eudragit RS 30 D* are less permeable to water. Film coatings prepared from both polymers give pH-independent release of active substance. Plasticizers are usually added to improve film properties.

Table III: Solubility of commercially available polymethacrylates in various solvents.

Type	Solvent					
	Acetone and alcohols ^(a)	Dichloromethane	Ethyl acetate	1 N HCl	1 N NaOH	Petroleum ether Water
<i>Eudragit</i> (Röhm GmbH)						
<i>Eudragit E</i> 12.5	M	M	M	M	—	M
<i>Eudragit E</i> 100	S	S	S	—	—	I
<i>Eudragit L</i> 12.5 P	M	M	M	—	M	P
<i>Eudragit L</i> 12.5	M	M	M	—	M	P
<i>Eudragit L</i> 100-55	S	I	I	—	S	I
<i>Eudragit L</i> 100	S	I	I	—	S	I
<i>Eudragit L</i> 30 D-55 ^(b) M ^(c)	—	—	—	M ^(d)	—	M
<i>Eudragit S</i> 12.5 P	M	M	M	—	M	P
<i>Eudragit S</i> 12.5	M	M	M	—	M	P
<i>Eudragit S</i> 100	S	I	I	—	S	I
<i>Eudragit RL</i> 12.5	M	M	M	—	—	P
<i>Eudragit RL</i> 100	S	S	S	—	—	I
<i>Eudragit RL</i> PO	S	S	S	—	I	I
<i>Eudragit RL</i> 30 D	M ^(e)	M	M	—	I	M
<i>Eudragit RS</i> 12.5	M	M	M	—	—	P
<i>Eudragit RS</i> 100	S	S	S	—	—	I
<i>Eudragit RS</i> PO	S	S	S	—	I	I
<i>Eudragit RS</i> 30 D	M ^(e)	M	M	—	I	M
<i>Eastacryl</i> (Eastman Chemical Company)						
<i>Eastacryl</i> 30D ^(b)	M ^(c)	—	—	—	M ^(d)	—
<i>Kollicoat</i> (BASF Fine Chemicals)						
<i>Kollicoat</i> MAE 30 D ^(b)	M ^(c)	—	—	—	M ^(d)	—
<i>Kollicoat</i> MAE 30 DP ^(b)	M ^(c)	—	—	—	M ^(d)	—

S = soluble; M = miscible; I = insoluble or immiscible; P = precipitates.

^(a) Alcohols including ethanol, methanol, and propan-2-ol.

^(b) Supplied as a milky-white aqueous dispersion.

^(c) A 1 : 5 mixture forms a clear, viscous, solution.

^(d) A 1 : 2 mixture forms a clear or slightly opalescent, viscous liquid.

^(e) 1 part of *Eudragit RL* 30 D or of *Eudragit RS* 30 D dissolves completely in 5 parts acetone, ethanol, or propan-2-ol to form a clear or slightly turbid solution. However, when mixed in a ratio of 1 : 5 with methanol, *Eudragit RL* 30 D dissolves completely, whereas *Eudragit RS* 30 D dissolves only partially.

Eudragit NE 30 D is an aqueous dispersion of a neutral copolymer consisting of polymethacrylic acid esters. The dispersions are milky-white liquids of low viscosity and have a weak aromatic odor. Films prepared from the lacquer swell in water, to which they become permeable. Thus, films produced are insoluble in water, but give pH-independent drug release.

Eudragit L 30 D-55, is an aqueous dispersion of an anionic copolymer based on methacrylic acid and ethyl acrylate. The copolymer corresponds to USPNF 20 methacrylic acid copolymer, Type C. The ratio of free-carboxyl groups to ester groups is 1 : 1. Films prepared from the copolymers dissolve above pH 5.5, forming salts with alkalis, thus affording coatings that are insoluble in gastric media but soluble in the small intestine.

Eastacryl 30D, *Kollicoat* MAE 30 D, and *Kollicoat* MAE 30 DP are also aqueous dispersions of the anionic copolymer based on methacrylic acid and ethyl acrylate. The copolymer also corresponds to USPNF 20 methacrylic acid copolymer, Type C. The ratio of free-carboxyl groups to ester groups is 1 : 1. Films prepared from the copolymers dissolve above pH 5.5, forming salts with alkalis, thus affording coatings that are insoluble in gastric media, but soluble in the small intestine.

Eudragit L 100-55 (prepared by spray-drying *Eudragit L* 30 D-55) is a white, free-flowing powder that is redispersible in

water to form a latex that has properties similar to those of *Eudragit L* 30 D-55.

9 Pharmacopeial Specifications

Specifications for polymethacrylates from the PhEur 2002 are shown in Table IV and those from the USPNF 20 in Table V.

10 Typical Properties

Acid value:

300–330 for *Eudragit L* 12.5, *L* 12.5 P, *L* 100, *L* 30 D-55, *L* 100-55; *Eastacryl* 30D; *Kollicoat* MAE 30 D, and *Kollicoat* MAE 30 DP

180–200 for *Eudragit S* 12.5, *S* 12.5 P, and *S* 100

Alkali value:

162–198 for *Eudragit E* 12.5 and *E* 100

23.9–32.3 for *Eudragit RL* 12.5, *RL* 100, and *RL* PO

27.5–31.7 for *Eudragit RL* 30 D

12.1–18.3 for *Eudragit RS* 12.5, *RS* 100, and *RS* PO

16.5–22.3 for *Eudragit RS* 30 D

Density (bulk): 0.390 g/cm³

Density (tapped): 0.424 g/cm³

Table IV: Specifications from PhEur 2002.

Test	PhEur 2002			
	Methacrylic acid-ethyl acrylate copolymer (1:1)	Methacrylic acid-ethyl acrylate copolymer (1:1) dispersion 30%	Methacrylic acid-methyl methacrylate copolymer (1:1)	Methacrylic acid-methyl methacrylate copolymer (1:2)
Identification	+	+	+	+
Characters	+	+	+	+
Appearance of a film	+	+	+	+
Apparent viscosity	+	≤ 15 mPa s	50–200 mPa s	—
Particulate matter	—	≤ 1.0%	—	—
Ethyl acrylate and methacrylic acid	≤ 0.1%	≤ 0.1%	—	—
Methyl methacrylate and methacrylic acid	—	—	≤ 0.1%	≤ 0.1%
Residue on evaporation	—	28.5–31.5%	—	—
Loss on drying	≤ 5.0%	—	≤ 5.0%	≤ 5.0%
Sulfated ash	≤ 0.4%	≤ 0.2%	≤ 0.1%	≤ 0.1%
Microbial contamination	—	+	—	—
Assay (methacrylic acid units)	46.0–50.6%	46.0–50.6%	46.0–50.6%	27.6–30.7%

Density (true):

0.811–0.821 g/cm³ for *Eudragit E*
 0.83–0.85 g/cm³ for *Eudragit L, S 12.5* and *12.5 P*
 0.831–0.852 g/cm³ for *Eudragit L, S 100*
 1.062–1.072 g/cm³ for *Eudragit L 30 D-55*
 0.821–0.841 g/cm³ for *Eudragit L 100-55*
 0.816–0.836 g/cm³ for *Eudragit RL* and *RS 12.5*
 0.816–0.836 g/cm³ for *Eudragit RL* and *RS PO*
 1.047–1.057 g/cm³ for *Eudragit RL* and *RS 30 D*
 1.037–1.047 g/cm³ for *Eudragit NE 30D*
 1.062–1.072 g/cm³ for *Eastacryl 30D*
 1.062–1.072 g/cm³ for *Kollicoat MAE 30 D* and *Kollicoat MAE 30 DP*

Refractive index:

$n_D^{20} = 1.38\text{--}1.385$ for *Eudragit E*
 $n_D^{20} = 1.39\text{--}1.395$ for *Eudragit L* and *S*
 $n_D^{20} = 1.387\text{--}1.392$ for *Eudragit L 100-55*
 $n_D^{20} = 1.38\text{--}1.385$ for *Eudragit RL* and *RS*

Solubility: see Table II.**Viscosity (dynamic):**

3–12 mPa s for *Eudragit E*
 ≤ 50 mPa s for *Eudragit NE 30D*
 50–200 mPa s for *Eudragit L* and *S*
 ≤ 15 mPa s for *Eudragit L 30 D-55*
 100–200 mPa s for *Eudragit L 100-55*
 ≤ 15 mPa s for *Eudragit RL* and *RS*
 ≤ 200 mPa s for *Eudragit RL* and *RS 30D*
 ≤ 15 mPa s for *Kollicoat MAE 30 D* and *Kollicoat MAE 30 DP*
 145 mPa s for *Eastacryl 30D*

11 Stability and Storage Conditions

Dry powder polymer forms are stable at temperatures less than 30°C. Above this temperature, powders tend to form clumps, although this does not affect the quality of the substance and the clumps can readily be broken up. Dry powders are stable for at least 3 years if stored in a tightly closed container at less than 30°C.

Dispersions are sensitive to extreme temperatures and phase separation occurs below 0°C. Dispersions should therefore be stored at temperatures between 5 and 25°C and are stable for at least 18 months after shipping from the manufacturer's

warehouse if stored in a tightly closed container at the above conditions.

12 Incompatibilities

Incompatibilities occur with certain polymethacrylate dispersions depending upon the ionic and physical properties of the polymer and solvent. For example, coagulation may be caused by soluble electrolytes, pH changes, some organic solvents, and extremes of temperature; see Table II. For example, dispersions of *Eudragit L 30 D*, *RL 30 D*, *L 100-55*, and *RS 30 D* are incompatible with magnesium stearate. *Eastacryl 30D*, *Kollicoat MAE 30 D*, and *Kollicoat MAE 30 DP* are also incompatible with magnesium stearate.

Interactions between polymethacrylates and some drugs can occur, although solid polymethacrylates and organic solutions are generally more compatible than aqueous dispersions.

13 Method of Manufacture

Prepared by the polymerization of acrylic and methacrylic acids or their esters, e.g., butyl ester or dimethylaminoethyl ester.

14 Safety

Polymethacrylate copolymers are widely used as film-coating materials in oral pharmaceutical formulations. They are also used in topical formulations and are generally regarded as nontoxic and nonirritant materials.

A daily intake of 2 mg/kg body-weight of *Eudragit* (equivalent to approximately 150 mg for an average adult) may be regarded as essentially safe in humans.

See also Section 15.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Additional measures should be taken when handling organic solutions of polymethacrylates. Eye protection, gloves, and a dust mask or respirator are recommended. Polymethacrylates should be handled in well-ventilated environment and measures should be taken to prevent dust formation.

Table V: Specifications from USP NF 20.

Test	USP NF 20	USP NF 20 (Suppl 1)
	Ammonio methacrylate copolymer ^(a)	Methacrylic acid copolymer
Identification	+	+
Viscosity		
Type A	≤ 15 mPa s	50–200 mPa s
Type B	≤ 15 mPa s	50–200 mPa s
Type C	—	100–200 mPa s
Loss on drying		
Type A	≤ 3.0%	≤ 5.0%
Type B	≤ 3.0%	≤ 5.0%
Type C	—	≤ 5.0%
Residue on ignition		
Type A	≤ 0.1%	≤ 0.1%
Type B	≤ 0.1%	≤ 0.1%
Type C	—	≤ 0.4%
Arsenic	—	≤ 2 ppm
Heavy metals	≤ 0.002%	≤ 0.002%
Organic volatile impurities	—	+
Limit of monomers	—	≤ 0.05%
Methyl methacrylate	≤ 0.005%	—
Ethyl acrylate	≤ 0.025%	—
Assay of methacrylic acid units (dried basis)		
Type A	8.85–11.96%	46.0–50.6%
Type B	4.48–6.77%	27.6–30.7%
Type C	—	46.0–50.6%

^(a) Corresponds to Eudragit RL and RS.

Acute and chronic adverse effects have been observed in workers handling the related substances methyl methacrylate and poly(methyl methacrylate) (PMMA).^(17,18) In the UK, the occupational exposure limit for methyl methacrylate has been set at 208 mg/m³ (50 ppm) long-term (8-hour TWA), and 416 mg/m³ (100 ppm) short-term.⁽¹⁹⁾

See also Section 17.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Methyl methacrylate; poly(methyl methacrylate).

Methyl methacrylate

Empirical formula: C₅H₈O₂

Molecular weight: 100.13

CAS number: [80-62-6]

Synonyms: methacrylic acid, methyl ester; methyl 2-methacrylate; methyl 2-methylpropenoate; MME.

Safety:

LD₅₀ (dog, SC): 4.5 g/kg

LD₅₀ (mouse, IP): 1 g/kg

LD₅₀ (mouse, oral): 5.2 g/kg

LD₅₀ (mouse, SC): 6.3 g/kg

LD₅₀ (rat, IP): 1.33 g/kg

LD₅₀ (rat, SC): 7.5 g/kg

Comments: methyl methacrylate forms the basis of acrylic bone cements used in orthopedic surgery.

Poly(methyl methacrylate)

Empirical formula: (C₅H₈O₂)_n

Synonyms: methyl methacrylate polymer; PMMA.

Comments: poly(methyl methacrylate) has been used as a material for intraocular lenses, for denture bases, and as a cement for dental prostheses.

18 Comments

A number of different polymethacrylates are commercially available that have different applications and properties; see Table II.

For spray coating, polymer solutions and dispersions should be diluted with suitable solvents. Some products need the addition of a plasticizer such as dibutyl sebacate, dibutyl phthalate, glyceryl triacetate, or polyethylene glycol. Different types of plasticizer may be mixed to optimize the polymer properties for special requirements.

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21 Authors

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22 Date of Revision

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